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Should Bacillus Calmette–Guérin (BCG) vaccine be used in the prophylaxis of COVID-19?

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KEY FINDINGS

At present, there is no sufficient evidence to support the use of BCG vaccine as prophylaxis for COVID-19.

- Bacillus Calmette Guerin (BCG) vaccine is an attenuated microorganism derived from bovine tubercle bacillus and is being given to prevent severe tuberculosis. It may enhance production of antibodies and pro-inflammatory cytokines such as interleukin (IL)-1 β and tumor necrosis factor (TNF).
- BCG may lead to increased CD4 and CD8 T-cell activity on subsequent viral infection.
- Ecological studies on the effect of BCG vaccination policy on COVID-19 outcomes have conflicting results and are prone to bias from confounders.
- There is insufficient evidence on the efficacy and safety of BCG vaccine for COVID-19 prophylaxis.
- Thirteen clinical trials are ongoing in healthcare workers, police officers and the elderly population to evaluate the efficacy and safety of BCG vaccine in preventing COVID-19 and its severe symptoms.
- WHO does not recommend the use of BCG vaccine as prophylaxis against COVID-19.
- Adverse events of BCG vaccine range from mild local cutaneous reactions to systemic adverse events such as abscess, lymphadenopathy and osteomyelitis.

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RESULTS

Available ecological studies have conflicting results. Majority of the studies have reported decreased incidence, mortality rates and case fatality rates for countries with BCG vaccination policy but did not factor into their analysis other variables that may affect COVID-19 outcomes such as population characteristics, level of testing, healthcare systems, control measures, burden of disease and stage of epidemic. In contrast, one study reported BCG coverage from 1981-1985 as proxy of coverage in 34-39-year-old cohort had no significant effect on crude growth rate and case fatality rates at the same stage of the epidemic (tenth day after cumulative cases exceeded 100 in a country). Three other studies reported BCG vaccination policy had no significant effect on COVID-19 mortality when confounders were considered in the analysis.

There are **no completed clinical trials** on BCG vaccine as prophylaxis for COVID-19. However, there are thirteen ongoing clinical trials (2 in Germany and Netherlands, 1 in Egypt, Colombia, United States of America, South Africa, Greece, Denmark, France, Canada, and Australia) investigating safety and efficacy of BCG vaccination in healthcare workers, police officers and the elderly population. Characteristics of these trials are summarized in Table 2.

CONCLUSION

Presently, there is insufficient evidence regarding the use of BCG vaccine as prophylaxis to COVID-19. The results of ongoing clinical trials are needed.

Declaration of Conflict of Interest

No conflict of interest

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Table 1. Characteristics of included studies

No.	Title/Author	Study design	Country	Population	Intervention Group(s)	Comparison Group(s)	Outcomes	Key findings
1	Correlation between universal BCG vaccination policy and reduced morbidity and mortality for COVID-19: an epidemiological study Miller A, Reandelar MJ, Fasciglione K, Roumenova V, Li Y, Otazu G	Population study	USA	Countries affected with COVID-19 with more than 1 million inhabitants	BCG vaccination policy	No BCG vaccination policy	Mortality rate	Lower mortality rates were reported for countries with BCG vaccination policy. Variability of mortality rates was noted for middle-high income countries with BCG vaccination policy.
2	BCG vaccination may be protective against COVID-19 Hegarty PK, Zafirakis H, Kamat A, Dinardo A	Population study	USA	Countries affected with COVID-19 (n=178)	BCG vaccination policy	No BCG vaccination policy	COVID-19 incidence Mortality rate	Countries with BCG vaccination program incidence: 38.4 per million mortality rate: 4.28 per million Countries without BCG vaccination program incidence: 358.4 per million mortality rate: 40 per million
3	Further Evidence of a Possible Correlation Between the Severity of Covid-19 and BCG Immunization Dolgikh S	Population study	Ukraine	Countries affected with COVID-19	BCG vaccination policy	No BCG vaccination policy	COVID-19 cases per capita COVID-19 mortality per capita	Italy, Spain, France, USA had severe COVID-19 disease compared to mild COVID-19 cases in Taiwan, Germany, many East European jurisdiction Vaccination level of different countries were correlated with the reported impact of COVID-19 on countries grouped according to mortality per capita (m.p.c.), which is a measure of epidemic impact. Countries in which the m.p.c. is <1 have universal immunization program (UIP) against tuberculosis Countries in which m.p.c. <10 have ongoing UIP against tuberculosis or has limited use (Canada, Norway). Countries who had never had a UIP or significant BCG immunization program have m.p.c. greater than or near 100. Time of cessation of UIP/BCG and the m.p.c. value of COVID-19 impact showed a significant correlation. The later the cessation of UIP/BCG, the lower the m.p.c. This, however, was not observed in Australia. Thus, further studies are suggested.

								<p>UIP/BCG offered at an older age (UK and possible France) have m.p.c. rates between 65-100. Portugal, Spain, Canada have regional variations in UIP/BCG.</p> <p>Areas where immunization was widely used have significantly lower COVID-19 cases such as Japan, South Korea, Taiwan and Singapore with a current BCG policy which have less severe COVID-19 impacts with m.p.c. in the range of <1% or lower.</p>
4	<p>Time-adjusted Analysis Shows Weak Associations Between BCG Vaccination Policy and COVID-19 Disease Progression</p> <p>Katarína Bodová, Vladimír Boža, Brona Brejová, et. al.</p>	Population study	Slovakia	40 countries- 12 with BCG status; 28 with no BCG status	Countries with recent universal BCG vaccination policies,	Countries with no BCG vaccination policies	<p>Case Fatality Rates in countries with BCG and no BCG</p> <p>Reproduction number of COVID-19 in BCG and no BCG countries</p>	<p>Countries with recent BCG vaccination showed a statistically significant lower Reproduction Number</p> <p>Death rate from COVID-19 was significantly lower in East Germany than West Germany</p> <p>No correlation between BCG vaccination policy and CFR</p>
5	<p>Association of national Bacille Calmette-Guérin vaccination policy with COVID-19 epidemiology: an ecological study in 78 countries</p> <p>Kuratani N</p>	Ecological study	Japan	78 countries	54 BCG countries	24 non-BCG countries	<p>Case Fatality Rates of COVID-19 in BCG and non-BCG countries</p> <p>Speed of COVID-19 increase in BCG and non-BCG countries</p>	<p>National BCG policy decreases in the country-specific risk of death by COVID-19</p> <p>Pooled CFR stratified by national BCG policy was significantly lower mortality in the BCG countries than in the non-BCG countries</p>
6	<p>Significantly Improved COVID-19 Outcomes in Countries with Higher BCG Vaccination Coverage: A Multivariable Analysis</p> <p>Danielle Klinger, Ido Blass, Nadav Rappoport, Michal Linial</p>	Population study	Israel	55 countries	Countries with current or past national mandatory vaccination policy (49 countries).	Countries that have only administered BCG vaccinations to specific groups at risk (6 countries)	<p>COVID-19 outcome and years of BCG administration</p> <p>Impact of recent vaccination</p> <p>Role of young population in the spread of COVID-19</p>	<p>Years of BCG administration, impact of recent vaccination, and the role of young population in the spread of COVID-19, are correlated with COVID-19 outcome</p>
7	<p>Does the Bacillus Calmette–Guérin vaccine provide protection from COVID-19?</p> <p>Soumya Roy</p>	Population study	India	50 countries	29 countries with universal BCG policy	21 countries without universal BCG policy	<p>Number of COVID-19 cases per 1M population in countries with BCG and no BCG policy</p>	<p>Countries with no BCG policy had a mean of 1272.9 cases per million with 80.7 deaths per million</p> <p>Countries with a universal BCG vaccination policy had a mean 131.2</p>

							Total number of deaths per 1M population in countries with BCG and no BCG policy	cases per million and 4 death per million population (P<0.001)
8	A study on the relationship between BCG vaccination and Covid-19 prevalence: Do other confounders warrant investigation? Mariita R, Musila J.	Population study	USA	Countries with COVID-19 cases	Countries with BCG vaccination policy	Countries without BCG vaccination policy	COVID-19 cases	BCG vaccination coverage had negative correlation with COVID-19 cases (R2=0.5707, p<0.0001). There was a strong association between low numbers of COVID-19 cases and BCG vaccination (mean value 75.54%). Other factors such as comorbidity, age and socioeconomic factors may influence the results.
9	Does BCG protect against SARS-CoV-2 infection?: elements of proof Ouanes Y, Bibi M, Baradai N, et al.	Epidemiological study	Tunisia	Countries with COVID-19 cases that did not meet the following exclusion criteria: Less than one million inhabitants Low-income countries Cases less than 500 Less than 500 tests per million performed	Countries with BCG vaccination policy Group A: low-middle income countries Group B: upper middle and high income	Countries that stopped or never had BCG vaccination policy Group C: upper middle and high income countries that had BCG vaccination policy but stopped Group D: Countries that never had BCG vaccination policy	Mortality Rd = deaths per million inhabitants/diagnostic tests per inhabitants	Upper middle and high income countries (group D) with no BCG vaccination policy had a significant higher mortality and higher Rd index compared to the other groups. Upper middle and high income countries with BCG vaccination policy (group B) had better survival than those that stopped their BCG vaccination policy (group C).
10	Epidemiological Determinants of Acute Respiratory Syndrome Coronavirus-2 Disease Pandemic and The Role of the Bacille-Calmette-Guerin Vaccine in Reducing Morbidity and Mortality Singh BR, Gandharva R, Karthikeyan R, et. al.	Population study	India	Countries with COVID-19 cases	Countries with BCG vaccination policy	Countries without BCG vaccination policy	Morbidity Mortality Case fatality rate	COVID-19 morbidity and mortality was decreased in countries with BCG vaccination policy. However, CFR showed no statistically significant difference.
11	Connecting BCG Vaccination and COVID-19: Additional Data Dayal D, Gupta S	Population study	India	Countries affected with COVID-19	BCG revaccination policy	High disease burden of COVID-19 with no BCG revaccination policy	COVID-19 case fatality rate	Mean CFR between the two groups of countries (5.2% versus 0.6%, p value <0.0001) with an RR 0.11, (95% CI:0.09-0.14)
12	The correlation between BCG immunization	Population study	Hongkong, China	Countries with COVID-19 cases with at least ten days data after	BCG immunization coverage for 1980-1985 as proxy of	No BCG immunization	Growth rate of confirmed cases Case fatality rate	No significant difference in the crude growth rate between countries with BCG coverage and countries without BCG

	coverage and the severity of COVID-19 Li Y, Zhao S, Zhuang Z, Cao P, Yang L, He D			cumulative confirmations exceed 100	BCG coverage among 34-39 years old cohort	coverage for 1980-1985		coverage (p-value=0.3948, two-sample-t-test). Countries with BCG coverage had a slightly higher growth rate of 8.56 versus 7.23 (increase in cumulative number over 10 days). The group of countries with BCG coverage had higher case-fatality-rate (CFR) than those without BCG coverage (0.022 versus 0.014), but the difference is not significant (pvalue=0.06). Countries without BCG coverage may have better medical conditions and living environment, thus, the lower growth rate and case fatality rate. No significant effects of BCG coverage (1980-1985, i.e., 34-39 age cohort when they were born) on the crude growth rate and case fatality rate on the tenth day after cumulative exceeding 100 in a country. Findings remained the same after extending to 20-day range and changing the threshold to 50 cases.
13	Evaluating the determinants of COVID-19 mortality: A cross-country study Jay Squalli	Cross-country Study	UAE	140 countries	Countries with BCG vaccination policy	Countries without BCG	COVID-19 mortality	No link between COVID-19 mortality and BCG vaccination
14	COVID-19 Related Mortality: Is the BCG Vaccine Truly Effective? Paredes JA, Garduno V, Torres J.	Population study	Mexico	High income countries with at least 1000 cases and at least 1 million inhabitants	Countries with BCG vaccination policy	Countries that never had BCG vaccination policy Countries with previous BCG vaccination policy	Mortality - Total deaths - Deaths at 1M - Deaths at 1000 th case	The mean number of deaths per 1 million population and the deaths at 1000 th case between countries with existing BCG vaccination policy and those without were not statistically significant.
15	Is there evidence that BCG vaccination has non-specific protective effects for COVID 19 infections or is it an illusion created by lack of testing? Shivendu S, Chakraborty S, et. al.	Population study	USA	Countries with COVID-19 cases	Countries with BCG vaccination policy	Countries without BCG vaccination policy	COVID-19 cases COVID-19 deaths	BCG vaccination policy had no significant effects on COVID-19 cases and mortality when COVID testing was taken into consideration.

Table 2. Characteristics of ongoing clinical trials

No.	Clinical Trial ID / Title	Status	Start and estimated primary completion date	Study design	Country	Population	Intervention Group(s)	Comparison Group(s)	Outcomes
1	Reducing Health Care Workers Absenteeism in Sars-Cov-2 Pandemic Through Bacillus Calmette-Guérin Vaccination, A Randomized Controlled Trial (BCG-CORONA) ClinicalTrials.gov Identifier: NCT04328441	Recruiting	Start date: 03/25/2020 Estimated primary completion date: 10/25/2020	Multicenter randomized controlled trial, placebo controlled	Netherlands	1000 nurses and physicians working at emergency rooms and wards where COVID-infected patients are treated	BCG vaccine 0.1 ml intracutaneously	Placebo: 0.1 ml of 0.9% NaCl intracutaneously	Primary: Number of days of unplanned absenteeism Secondary: Incidence of documented SARS-CoV-2 infection Incidence of severe respiratory symptoms, hospital admission, intensive care admission and death from SARS-CoV-2 infection Number of days of fever, respiratory symptoms Incidence of SARS-CoV-2 antibodies
2	BCG Vaccination to Protect Healthcare Workers Against COVID-19 (BRACE) ClinicalTrials.gov Identifier: NCT04327206	Recruiting	Start date: 03/30/2020 Estimate primary completion date: 10/30/2020	Multicenter, open label randomized controlled trial	Australia	4000 healthcare workers in hospital sites	BCG vaccine 0.1 ml Intradermally	None	Primary: Incidence of COVID-19 disease and severe COVID-19 disease Secondary: Time to first symptom and duration of symptoms of COVID-19 Work absenteeism Hospital admission, critical care admission Need for oxygen therapy, mechanical ventilation Mortality Local and systemic adverse events to BCG

3	Application of BCG Vaccine for Immune-prophylaxis Among Egyptian Healthcare Workers During the Pandemic of COVID-19 ClinicalTrials.gov Identifier: NCT04350931	Not yet recruiting	Start date: 04/20/2020 Estimate primary completion date: 10/01/2020	Multicenter randomized controlled trial, placebo controlled	Egypt	900 healthcare workers at emergency rooms, ICUs and wards of isolation hospitals	BCG vaccine 0.1 ml Intradermally	Placebo: 0.1 ml of 0.9% NaCl intradermally	Primary: incidence of confirmed COVID-19 Secondary: Number of days of absenteeism Incidence of hospital admission Incidence of ICU admission Mortality
4	Performance Evaluation of BCG Vaccination in Healthcare Personnel to Reduce the Severity of SARS-COV-2 Infection ClinicalTrials.gov Identifier: NCT04362124	Not yet recruiting	Start date: 04/2020 Estimate primary completion date: 06/2021	Multicenter, randomized controlled trial	Colombia	1000 healthcare workers directly involved in the care of COVID-19 patients	BCG vaccine 0.1 ml Intradermally	Placebo: 0.1 ml of 0.9% NaCl intradermally	Primary: incidence of confirmed and probable COVID-19 cases Secondary: Incidence of severe COVID-19 infection Mortality Safety of BCG vaccination (adverse events)
5	BCG Vaccine for Health Care Workers as Defense Against COVID 19 (BADAS) ClinicalTrials.gov Identifier: NCT04348370	Recruiting	Start date: 04/20/2020 Estimate primary completion date: 05/2021	Multicenter randomized controlled trial	USA	1800 healthcare workers involved in the care of suspected and confirmed COVID-19 patients with at least 25 hours per week of direct patient care	BCG vaccine 0.1 ml Intradermally	Placebo: 0.1 ml of 0.9% NaCl intradermally	Primary: incidence of COVID-19 infection Secondary: Disease severity (Covid Severity Scale Scoring)
6	Reducing COVID-19 Related Hospital Admission in Elderly by BCG Vaccination ClinicalTrials.gov Identifier: NCT04417335	Active, not recruiting	Start date: 04/16/2020 Estimate primary completion date: 05/2021	Placebo-controlled adaptive multi-center randomized controlled trial	Netherlands	2014 Elderly people (≥ 60 years of age)	BCG vaccine	Placebo: 0.9% NaCl	Primary: SARS-CoV-2 related hospital admission Secondary Duration of hospital stay Cumulative incidence of infection, symptoms, intensive care admission and death
7	BCG Vaccination for Healthcare Workers in COVID-19 Pandemic ClinicalTrials.gov Identifier: NCT04379336	Recruiting	Start date: 05/04/2020 Estimate primary completion date:	Randomized controlled trial, placebo controlled	South Africa	500 healthcare workers	BCG vaccine 0.1 ml intradermally	Placebo: 0.1 ml of 0.9% NaCl intradermally	Primary: Incidence of healthcare workers admitted due to COVID-19 Secondary:

			04/28/2021						<p>Incidence of SARS-CoV-2 infection</p> <p>Incidence of upper respiratory tract infection</p> <p>Incidence of ICU admission</p> <p>Incidence of death</p> <p>Days of unplanned absenteeism due to COVID-19</p> <p>Prevalence of latent TB infection</p> <p>Incidence of active TB</p> <p>Incidence of adverse events</p>
8	<p>Bacillus Calmette-guérin Vaccination to Prevent COVID-19 (ACTIVATEII)</p> <p>ClinicalTrials.gov Identifier: NCT04414267</p>	Recruiting	<p>Start date: 05/26/2020</p> <p>Estimate primary completion date: 05/25/2021</p>	Prospective randomized open-label controlled trial	Greece	900 elderly patients hospitalized at the 4th Department of Internal Medicine of ATTIKON University General Hospital	BCG vaccine 0.1 ml intradermally	Placebo: 0.1 ml of 0.9% NaCl intradermally	<p>Primary: Positive for the respiratory questionnaire on appearance of COVID-related symptoms</p> <p>Positive IgM or IgG antibodies against SARS-CoV-2</p>
9	<p>Using BCG Vaccine to Protect Health Care Workers in the COVID-19 Pandemic</p> <p>ClinicalTrials.gov Identifier: NCT04373291</p>	Not yet recruiting	<p>Start date: 05/2020</p> <p>Estimate primary completion date: 12/2020</p>	Multi-center randomized placebo-controlled trial	Denmark	1500 healthcare workers with direct patient contacts; nurses, physicians and other medical staff working at emergency rooms or wards where COVID-19 patients are treated	BCG vaccine 0.1 ml intradermally	Placebo: 0.1 ml of 0.9% NaCl intradermally	<p>Primary: Number of days of unplanned absenteeism for any reason</p> <p>Secondary: Cumulative incidence of COVID infection, hospital admission, ICU admission, days of unplanned absenteeism due to COVID</p>
10	<p>Efficacy of BCG Vaccination in the Prevention of COVID19 Via the Strengthening of Innate Immunity in Health Care Workers (COVID-BCG)</p> <p>ClinicalTrials.gov Identifier: NCT04384549</p>	Not yet recruiting	<p>Start date: 05/11/2020</p> <p>Estimate primary completion date: 02/11/2021</p>	Randomized, multicenter, phase III, controlled trial	France	1120 healthcare workers	BCG vaccine 0.1 ml intradermally	Placebo: 0.1 ml of 0.9% NaCl intradermally	<p>Primary: Incidence of COVID-19 infection</p> <p>Secondary: Number of patients requiring ICU admission, oxygen, ECMO or artificial ventilation</p>

									Incidence of asymptomatic COVID-19 Incidence of respiratory infection Number of sick days and sick leaves BCG-related adverse events Changes in innate immune markers
11	Efficacy and Safety of VPM1002 in Reducing SARS-CoV-2 (COVID-19) Infection Rate and Severity (COBRA) ClinicalTrials.gov Identifier: NCT04439045	Not yet recruiting	Start date: 06/14/2020 Estimate primary completion date: 04/01/2021	Double-blind, randomized controlled trial	Canada	3626 front-line police officers	Recombinant BCG vaccine 0.1 ml intradermally	Placebo: 0.1 ml of 0.9% NaCl intradermally	Primary: COVID-19 infection Secondary: Incidence of hospitalization, ICU admission, ARDS, mechanical ventilation, secondary infection, mortality and innate trained immunity Adverse events
12	Study to Assess VPM1002 in Reducing Healthcare Professionals' Absenteeism in COVID-19 Pandemic ClinicalTrials.gov Identifier: NCT04387409	Recruiting	Start date: 05/25/2020 Estimate primary completion date: 06/30/2021	Phase III, Double-blind, Randomized, Placebo-controlled Multicentre Clinical Trial	Germany	1200 healthcare professionals (doctors, nurses, paramedical staff) working in emergency departments, ICU, infectious disease wards, COVID-19 wards, isolation wards	Recombinant BCG vaccine 0.1 ml intradermally	Placebo: 0.1 ml of 0.9% NaCl intradermally	Primary: Number of days absent from work due to respiratory disease Secondary: Incidence of COVID-19 related symptoms, SARS-CoV-2 infection, mortality, ICU admission, hospital admission,
13	Study to Assess VPM1002 in Reducing Hospital Admissions and/or Severe Respiratory Infectious Diseases in Elderly in COVID-19 Pandemic ClinicalTrials.gov Identifier: NCT04435379	Recruiting	Start date: 06/2020 Estimate primary completion date: 05/31/2021	Phase III, Randomized, Double-blind, Placebo-controlled, Multicentre, Clinical Trial	Germany	2038 adults aged 60 and above	Recombinant BCG vaccine 0.1 ml intradermally	Placebo: 0.1 ml of 0.9% NaCl intradermally	Primary: Number of days with severe respiratory disease Secondary: Cumulative incidence of hospital admissions, SARS-CoV-2 infection, respiratory symptoms, hospital admission, ICU admission, mortality

										Number of days with COVID-19 related symptoms
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